Original Study

Effect of Metformin Use on Survival Outcomes in Patients With Metastatic Renal Cell Carcinoma

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Abstract

In light of the emerging evidence of the antineoplastic potential of metformin, we investigated its effect on survival outcomes in metastatic renal cell carcinoma using a large clinical trial database. Although metformin did not affect survival in the overall cohort, it conferred a survival advantage in diabetic metastatic renal cell carcinoma patients treated with sunitinib.

Introduction: Observational studies have suggested that metformin use is associated with favorable outcomes in several cancers. For renal cell carcinoma (RCC), data have been limited. Therefore, we investigated the effect of metformin on survival in metastatic RCC (mRCC) using a large clinical trial database. **Patients and Methods:** We conducted a retrospective analysis of patients with mRCC in phase II and III clinical trials. The overall survival (OS) in metformin users was compared with that of users of other antidiabetic agents and those not using antidiabetic agents. Progression-free survival, objective response rate, and adverse events were secondary endpoints. Subgroup analyses were conducted after stratifying by class of therapy, type of vascular endothelial growth factor tyrosine kinase inhibitors, and International Metastatic RCC Database Consortium (IMDC) risk groups. **Results:** We identified 4736 patients with mRCC, including 486 with diabetes, of whom 218 (4.6%) were taking metformin. Metformin use did not affect OS when compared with users of other antidiabetic agents or those without diabetes. Furthermore, metformin use did not confer an OS advantage when stratified by class of therapy and IMDC risk group. However, in diabetic patients receiving sunitinib (n = 128), metformin use was associated with an improvement in OS compared with users of other antidiabetic agents (29.3 vs. 20.9 months, respectively; hazard ratio, 0.051; 95% confidence interval, 0.009-0.292; $P = .0008$). **Conclusion:** In the present study, we found a survival benefit for metformin use in mRCC patients treated with sunitinib. Clinical and preclinical studies are warranted to validate our results and guide the use of metformin in the clinic.

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Introduction

Type 2 diabetes mellitus (DM) affects 28.9 million people in the United States, comprising 12.3% of the adult population.[1] DM is common among cancer patients, with prevalence rates ranging from 8% to 18%.[2] The high prevalence of DM in cancer is associated with the increasingly aging population, the obesity epidemic in the United States, and the increased cancer risk with DM.[3-6] Epidemiologic studies have shown that DM is associated with an increased risk of renal cell carcinoma (RCC) incidence, recurrence, and mortality.[3,7-9]

Metformin, a biguanide hypoglycemic agent, has been prescribed extensively for > 30 years to treat patients with type 2 DM.[10,11] In addition to its wide use as an antidiabetic drug, recent evidence has demonstrated its role as a potential antineoplastic agent. Some observational studies have shown that metformin reduces cancer risk and recurrence and increases survival in several malignancies, including breast, colorectal, lung, prostate, and endometrial cancers.[12,13] However, the results have been controversial, given the inconsistencies among the existing studies. In RCC, studies of the effect of metformin on survival outcomes have been limited to small retrospective series, most of which have failed to show a clinical benefit.[14,15] Experimental studies have highlighted the antineoplastic activity of metformin in several cancers, including RCC.

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Metformin inhibited the proliferation of RCC cell lines and tumor xenografts in preclinical models. The inhibitory effect of metformin is hypothesized to occur through activation of the AMP-activating protein kinase (AMPK) pathway and lowering of the insulin levels.[16-18]

We investigated the effect of metformin on overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in a large clinical trial database of patients with metastatic renal cell carcinoma (mRCC).

Patients and Methods

Study Design

We conducted a retrospective survival analysis of patients with mRCC treated in phase II clinical trials (ClinicalTrials.gov identifiers, NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423, and NCT00835978) and phase III clinical trials (ClinicalTrials.gov identifiers, NCT00083889, NCT00065468, NCT000678392, NCT00474786, NCT00631371, and NCT00920816) sponsored by Pfizer. Eligible patients had a diagnosis of mRCC of any histologic subtype.

Baseline demographic, clinical, and laboratory data were collected for all the patients from the case report forms. The medication data collected included the following: treatment type, reason for treatment, start date, end date, and whether the use was ongoing. It was individually reviewed by our pharmacist (K.M.) to confirm accurate designation of metformin use. The patients were grouped into 3 cohorts, depending on the baseline use of antidiabetic treatment as follows: metformin users, users of other antidiabetic agents, and nonusers of antidiabetic therapy.

Treatment Outcomes

OS was defined as the time from randomization for randomized studies and from the initiation of therapy for nonrandomized studies to death from any cause. PFS was defined as the time from randomization for randomized studies and from the initiation of therapy for nonrandomized studies to the date of progression or death from any cause, whichever came first. The response was assessed using the Response Evaluation Criteria In Solid Tumors, version 1.0.

Statistical Analysis

The primary objective of the present study was to evaluate OS for patients receiving metformin compared with patients treated with other antidiabetic therapies or no antidiabetic therapy. PFS, ORR, and adverse events (AEs) were secondary endpoints. OS and PFS were estimated using the Kaplan-Meier method and were assessed using multivariate Cox regression analysis, adjusting for age, gender, race, Eastern Cooperative Oncology Group performance status, histologic type, International Metastatic RCC Database Consortium (IMDC) risk criteria, baseline creatinine level, previous nephrectomy, previous therapy, sites of metastasis, baseline hypertension, baseline statin use, and baseline angiotensin system inhibitor use. All P values were 2 sided. Subgroup analyses were conducted by the class of mRCC therapy (vascular endothelial growth factor [VEGF]-targeted therapy, mammalian target of rapamycin [mTOR]-targeted therapy, and interferon-alfa therapy), type of VEGF-tyrosine kinase inhibitor (TKI; sunitinib, axitinib, and sorafenib), and IMDC risk group (favorable, intermediate, and poor risk). Treatment-associated toxicities were defined and evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0. Frequent serious (grade ≥ 3) AEs occurring in $> 3\%$ of patients were summarized.

The statistical analyses were predefined at the inception of the project, although the study itself was a post hoc analysis of prospectively collected data. The analyses were conducted using SAS.

Results

Patient Characteristics and Treatment Exposure

We identified 4736 patients treated with first-line or second-line therapy for mRCC from January 2003 to June 2013. The median age at diagnosis was 61.5 years, with most patients (66.5%) < 65 years (Table 1). The patients were mostly men (71.0%), were of white ethnicity (77.4%), and had a good performance status (52.7%). Clear cell RCC was the dominant histologic type (89.4%), and the lung was the most common site of metastasis (76.6%). Most of the patients had undergone previous nephrectomy (70.2%) and a few had received previous therapy (33.2%). The IMDC risk was favorable, intermediate, and poor in 13.6%, 42.4%, and 24.1% of the patients, respectively.

Of the 4736 patients analyzed, 644 (13.6%) were categorized as "diabetic," and 486 patients (10.3% of the total cohort and 73.2% of the diabetic patients) received antidiabetic treatment. The patients with type 2 DM were grouped as metformin users (n = 218) and users of other antidiabetic therapies (n = 268). The other antidiabetic therapies included insulin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide agonists (Supplemental Table 1 in the online version). Most of the antidiabetic therapy users had hypertension (75.2% and 73.5% of the metformin and other antidiabetic users, respectively), in contrast to the nonusers of antidiabetic therapy, of whom only 41.5% of patients had hypertension. The baseline patient and disease characteristics were similar across the 3 cohorts, except for the baseline medical conditions, including DM and hypertension, and concomitant use of statins and angiotensin system inhibitors, for which we adjusted in our analyses.

The patients were treated with sunitinib (n = 1059, 22.4%), axitinib (n = 896, 18.9%), bevacizumab-containing regimens (n = 784, 16.6%), sorafenib (n = 772, 16.3%), temsirolimus-containing regimens (n = 665, 14.0%), and IFN-alfa (n = 560, 11.8%) (Supplementary Table 2 in the online version). A total of 3511 patients (74.1%) received VEGF-targeted therapy, with sunitinib the most prevalent treatment (n = 1059, 22.4%). Of the patients receiving antidiabetic therapy, most (67.7%) received first-line therapy.

Effect of Metformin on Survival

In the overall cohort, metformin use did not affect OS or PFS compared with patients who used other antidiabetic therapy (OS: hazard ratio [HR], 0.771; 95% confidence interval [CI], 0.566-1.049; $P = .0980$; PFS: HR, 0.905; 95% CI, 0.682-1.199; $P = .4858$) or patients who did not use antidiabetic therapy (OS: HR, 1.053; 95% CI, 0.837-1.324; $P = .6606$; PFS: HR, 0.979; 95% CI, 0.806-1.189; $P = .8274$; Table 2, Figure 1).